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RICHARD ARON OSMAN
3525 Del Mar Heights Rd. #915
San Diego, CA 92130

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NOAKES, SUZANNE MARIE	
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte KEVIN H. GARDNER, CARLOS A. AMEZCUA,
PAULUS J. A. ERBEL, and PAUL B. CARD

Appeal 2009-009581
Application 10/677,733
Technology Center 1600

Decided: November 4, 2009

Before TONI R. SCHEINER, DEMETRA J. MILLS, and
RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on the appeal by the patent applicants from the patent examiner's rejection of claims 3 and 5. The Board has jurisdiction for this appeal is under 35 U.S.C. § 6(b). We reverse.

STATEMENT OF THE CASE

The appealed claims are to methods of using NMR spectra to determine the presence of a ligand specifically bound to the hydrophobic core of a PAS domain. PAS domains are protein interaction domains used in intra- and intermolecular associations (Spec. 1). The term "PAS" was derived from the first letters of the Per, ARNT (aryl hydrocarbon receptor nuclear translocator), and Sim proteins which were used to originally define the domain.

Claims 3 and 5 are appealed and stand rejected by the Examiner under 35 U.S.C. § 103(a) as obvious over Fesik (WO 97/18471, May 27, 1997) in view of Edery (US 5,843,683, Dec. 1, 1998), Takahashi (US 6,291,429 B1, Sep. 18, 2001), or Berkenstam (US 6,436,654 B1, Aug. 20, 2002).

Claim 3 is representative and reads as follows:

> 3. A method of detecting binding of a PAS (Per-ARNT-Sim) domain of a protein with a foreign core ligand of the PAS domain, wherein the PAS domain is prefolded in its native state, the method comprising the steps of:
>
> determining from NMR analysis of the PAS domain that the PAS domain comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity;
>
> detecting a first NMR spectrum of the PAS domain in the presence of the foreign ligand;
>
> comparing the first NMR spectrum with a second NMR spectrum of the PAS domain in the absence of the ligand; and therefrom
>
> determining the presence of the ligand specifically bound within the hydrophobic core of the PAS domain.

STATEMENT OF THE ISSUE

The issue in this appeal is whether persons of ordinary skill in the art would have reasonably expected that the NMR ligand binding assay

described in the Fesik publication would have detected ligands which bind to a PAS domain having a hydrophobic core with no apparent a priori formed ligand cavity.

PRINCIPLES OF LAW

35 U.S.C. § 103(a):

> A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

"Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, inter alia, consideration of . . . whether the prior art would also have revealed that in so making or carrying out [the claimed invention], those of ordinary skill would have a reasonable expectation of success." *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991).

FINDINGS OF FACT

Fesik

1. Fesik describes a process for identifying compounds which bind to a specific target molecule (Abstract).
2. The method involves generating two NMR spectra of a target molecule, before and after exposure to a mixture of compounds (Abstract).
3. The two spectra are compared to identify differences between them. The differences are used to identify "the presence of one or more compounds that are ligands which have bound to the target molecule." (Abstract.)
4. The preferred target molecule is a polypeptide (2:20-21).

Edery

5. Edery teaches that abnormalities in the conserved protein domain, PAS, can cause certain conditions or diseases in humans (col. 1, ll. 40-44).

6. According to Edery, PAS proteins have binding affinities for one another and are able to form dimers with identical proteins or different proteins that contain PAS domains (col. 5, ll. 24-25). Edery "describes methods for identifying compounds that may promote or interfere with these PAS-PAS binding affinities." (Col. 5, ll. 33-34; *see also* col. 8, l. 65 to col. 9, l. 31; col. 12 (Example 4).)

7. Edery describes:

> an in vitro assay method for identifying, screening and characterizing compounds potentially useful for treatment of diseases or disorders arising from abnormal PAS-PAS binding affinities. This method includes bringing together a test sample and a PAS-containing protein preparation. The test sample contains one or more test compounds, and the PAS-containing protein preparation contains one or more human peptides comprising at least the PAS region being investigated. The test sample is incubated with the PAS-containing protein preparation under conditions that would allow the PAS domain containing proteins to interact in the absence of the test sample. Those test samples containing one or more test compounds that affect PAS-containing protein binding functions can then be identified.

(Col. 3, ll. 31-46.)

Berkenstam

8. HIF-1α contains a PAS domain (col. 7, ll. 55-56).

9. Berkenstam describes assays to identify compounds which modulate the function of HIF-1α (col. 1, 11-15).

10. A candidate compound is contacted with a HIF-1α variant and "the effect of the candidate compound on the said variant" is determined (col. 7, l. 66-67).

11. The compound can effect the cellular localization of HIF-1α or the ability of HIF-1α to regulate a reporter gene (col. 8, ll. 1-15).

Takahashi

12. Takahashi describes mammalian CLOCK polypeptides which contain PAS domains (col. 7, ll. 30-55).

13. Takahashi teaches that CLOCK interacts directly with DNA (col. 7, ll. 55-57).

14. The PAS domains "are further known to be protein dimerization domains and indicate that CLOCK can interact with itself or with other HLH-PAS domain family members." (Col. 7, ll. 58-60.)

15. Takahashi describes a "screening assay for the identification of drugs or compounds that inhibit the action of CLOCK polypeptide (e.g., DNA binding)." (Col. 9, 15-17.)

ANALYSIS

It is undisputed that the difference between Fesik and the method recited in claim 3 is that Fesik does not teach the claimed step of "determining from NMR analysis of the PAS domain that the PAS domain comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity" nor applying its method to identify ligands which specifically bind to the recited PAS hydrophobic core. The Examiner found that each of Edery, Berkenstam, and Takahashi would have provided the ordinary skilled worker with the reason to have used Fesik's method with proteins containing PAS domains because the former taught that modulators of the PAS domain

are useful to prevent and treat diseases (Ans. 6). Appellants contend that the Examiner erred in concluding that it would have been obvious to have utilized Fesik's method to find ligands which bind to a PAS domain comprises a hydrophobic core with no apparent ligand cavity (Reply Br. 7). Appellants' position is supported by the totality of evidence before us.

The Examiner cited the Edery, Takahashi, and Berkenstam publications for teaching modulators of the PAS domain (Ans. 6 & 10). However, as established by Appellants, these references do not teach that the modulators bind to the PAS hydrophobic core as required by claim 3. Edery teaches identifying compounds which regulate the binding between PAS domains from different proteins (FF6-7); there is no evidence that this interaction involves the PAS core. Takahashi describes protein dimerization and DNA binding as characteristic of its PAS containing CLOCK protein (FF13-14). Takahashi specifically mentions identifying compounds that inhibit the DNA binding activity (FF15). There is no evidence that compounds which regulate either CLOCK protein dimerization or DNA binding involve the core of the PAS domain. Berkenstam also discloses assays which modulate a protein with a PAS domain (FF8-11). However, as with the Edery and Takahashi references, there is no information in Berkenstam that its assay was designed to detect compounds which bind to the PAS domain core. Thus, the cited references do not support the finding that persons of ordinary skill in the art would have reasonably expected that Fesik's method would be useful to determine "the presence of the ligand specifically bound within the hydrophobic core of the PAS domain" as recited in the last step of claim 3.

To further buttress their argument, Appellants provided two declarations, one by Dr. Stephen R. Sprang ("Sprang Dec.) and the other by Dr. Kevin H. Gardner ("Gardner Dec."). Dr. Sprang is a professor at the University of Texas who has authored numerous papers on protein structure and regulation (Sprang Dec. ¶ 1). Dr. Gardner is a co-inventor of the application and also a professor who has "authored numerous scientific papers in the field of NMR analyses of protein structure, function and regulation." (Gardner Dec. ¶ 1). There is no dispute that Drs. Sprang and Gardner are persons of ordinary skill in the field which is pertinent to the claimed invention. In each declaration, the declarant testified that persons of ordinary skill in the art would not have expected that a ligand would be bound within the PAS hydrophobic core.

Dr. Sprang testified that Fesik's method had been used with proteins which have preformed ligand binding pockets (Sprang Dec. ¶ 2). In contrast, Dr. Sprang stated that "the recited PAS domains are determined to be absent any ligand binding pocket, and such proteins have not been, and would not have been screened for ligand binding by NMR because based on their structure." (Sprang Dec. ¶ 3.) For this reason, Dr. Sprang concluded that:

> one skilled in the art would not have suspected that such PAS domains (without known cofactors and having tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligand binding site) would be rational candidates to screen for core ligand binding; in fact, the prior art teaches squarely away from such use.

(Sprang Dec. ¶ 6.)

Dr. Gardner testified that targeting the PAS hydrophobic core with Fesik's method would have been "a non-obvious route for an ordinarily

skilled worker in the field." (Gardner Dec. ¶ 6.) For similar reasons to those stated by Dr. Sprang, Dr. Gardner states that "without an a priori formed cavity there would be an overwhelming expectation that our targeted core ligand binding sites would not even exist." (*Id.*)

The Examiner asserted that the declarations were insufficient to rebut the rejection because it was known that ligands or cofactors were required by many PAS domains, and that therefore persons of ordinary skill in the art would have reasonably believed that the claimed PAS proteins with hydrophobic cores would be rationale candidates for Fesik's method (Ans. 13-14).

The Examiner's argument is not persuasive. As argued by Appellants, the Specification specifically discloses that certain PAS domains are known to contain small molecules within their core (Spec. 1). However, this is not the case for PAS domains with hydrophobic cores and with no NMR apparent formed ligand cavity, the class of PAS-containing proteins which is claimed (Spec. 2; App. Br. 2-3). Neither Edery, Berkenstam, nor Takahashi support the Examiner's position since these references do not describe a compound bound to a PAS hydrophobic core or a method of targeting the core.

Obviousness is evaluated from the perspective of a person ordinary skill in the art. 35 U.S.C. § 103(a). In this case, Appellants provided testimony from two persons of ordinary skill in the art that Fesik's method would not have reasonably been expected to have determined "the presence of . . . ligand specifically bound within the hydrophobic core of the PAS domain" as recited in claim 3. The Examiner did not provide sufficient

reason or evidence to doubt their testimony. Accordingly, we shall reverse the rejection.

CONCLUSION OF LAW & SUMMARY

Persons of ordinary skill in the art would not have reasonably expected that the NMR ligand binding assay described in Fesik would have detected ligands which bind to a PAS domain having a hydrophobic core with no NMR-apparent a priori formed ligand cavity as required by claim 3. The rejection of claim 3 is reversed. The rejection of claim 5 is also reversed because it depends on claim 3 and incorporates all its limitations.

REVERSED

dm

RICHARD ARON OSMAN
4070 CALLE ISABELLA
SAN CLEMENTE, CA 92672